Hines, J.
09/308829

-key terms

```
     FILE 'CAPLUS' ENTERED AT 14:01:39 ON 24 SEP 1999
L1             0 SEA ABB=ON  PLU=ON  ((STREPTOCOC? OR S)(W)PRYROGEN?(W)(EX
                 OTOXIN OR EXO TOXIN))(3A)C
L2            35 SEA ABB=ON  PLU=ON  ((STREPTOCOC? OR S)(1W)(EXOTOXIN OR
                 EXO TOXIN))(3A)C
L3            44 SEA ABB=ON  PLU=ON  (SPEC OR SPE C)(S)STREPTOCOC?
L4             2 SEA ABB=ON  PLU=ON  (L2 OR L3)(S)(MUTAT? OR MUTAGEN? OR
                 MUTANT OR POLYMORPH? OR POLY(W)(MORPHISM OR MORPHIC?))
L5             4 SEA ABB=ON  PLU=ON  (L2 OR L3) AND (MUTAT? OR MUTAGEN?
                 OR MUTANT OR POLYMORPH? OR POLY(W)(MORPHISM OR MORPHIC?))

L6             4 SEA ABB=ON  PLU=ON  L4 OR L5

L6   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 1999 ACS
ACCESSION NUMBER:         1998:649642  CAPLUS
DOCUMENT NUMBER:          130:13058
TITLE:                    Mutational analysis of superantigen
                          activity responsible for the induction of skin
                          erythema by streptococcal pyrogenic
                          exotoxin C
AUTHOR(S):                Yamaoka, Junichi; Nakamura, Eijiro; Takeda,
                          Yoshifumi; Imamura, Sadao; Minato, Nagahiro
CORPORATE SOURCE:         Department of Dermatology, Graduate School of
                          Medicine, Kyoto University, Kyoto, 606-8501,
                          Japan
SOURCE:                   Infect. Immun. (1998), 66(10), 5020-5026
                          CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER:                American Society for Microbiology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Streptococcal pyrogenic exotoxin C (
     SPEC), when injected intradermally, induces erythema in
     unsensitized rabbits. In the present study, we examd. whether this
     erythema induction is due to the T-cell stimulatory activity of SPEC
     as a superantigen. Anal. by using single-residue mutant
     SPECs indicated that mutant SPECs Y15I, A16E, and Y17I, in
     which tyrosine 15, alanine 16, and tyrosine 17 were replaced with
     isoleucine, glutamic acid, and isoleucine, resp., exhibited
     significantly reduced mitogenic activity for V.beta.2+ human T cells
     in vitro, and Y15I showed as much as a 1,000-fold redn. Y15I
     mutant SPEC, however, retained the ability to bind to major
     histocompatibility complex class II antigen and to form a homodimer,
     implying that residue 15 is critically important for the interaction
     of SPEC with T-cell antigen receptor .beta. chains. When injected
     intradermally into normal rabbits, wild-type SPEC induced a
     characteristic erythema after 3 h in a dose-dependent fashion, which
     was assocd. with polymorphonuclear and mononuclear cell
     infiltration. This erythema formation was found to be severely
     suppressed by systemic pretreatment with cyclosporin A, suggesting
```

the involvement of host T cells. Y15I **mutant** SPEC exhibited nearly 1,000-fold less erythema induction in vivo than wild-type SPEC. Altogether, the present results strongly suggest that erythema induction in rabbits by SPEC is attributable mostly to its T-cell stimulatory activity as a superantigen.

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:398420 CAPLUS
DOCUMENT NUMBER: 129:53355
TITLE: **Mutants** of streptococcal toxin C and use as vaccines
INVENTOR(S): Schlievert, Patrick M.; Ohlendorf, Douglas; Mitchell, David T.; Gahr, Pamala J.
PATENT ASSIGNEE(S): Regents of the University of Minnesota, USA; Schlievert, Patrick M.; Ohlendorf, Douglas; Mitchell, David T.; Gahr, Pamala J.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9824910	A2	19980611	WO 1997-US22125	19971205
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9876256	A1	19980629	AU 1998-76256	19971205
PRIORITY APPLN. INFO.:			US 1996-33251	19961206
			WO 1997-US22125	19971205

AB This invention is directed to **mutants** of **Streptococcus** pyrogenes **exotoxin** type **C** (**SPE-C**) or fragments thereof, vaccine and pharmaceutical compns., and methods of using the vaccine and pharmaceutical compns. The preferred SPE-C toxin has at least one amino acid change and is substantially non-lethal compared with the wild type SPE-C toxin. The **mutant** SPE-C toxins can form vaccine compns. useful to protect animals against the biol. activities of wild type SPE-C toxin. Single and double substitution **mutants** of SPE-C were prepd. with E. coli. Rabbits immunized with these recombinant toxins were protected from

challenge by S. pyogenes.

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1995:10032 CAPLUS
DOCUMENT NUMBER: 122:73341
TITLE: Molecular evolution of the staphylococcal and streptococcal pyrogenic toxin gene family
AUTHOR(S): Van Den Bussche, Ronald A.; Lyon, Julie D.; Bohach, Gregory A.
CORPORATE SOURCE: Dep. Biol. Sci., Univ. Idaho, Moscow, 83843, Russia
SOURCE: Mol. Phylogenet. Evol. (1993), 2(4), 281-92
CODEN: MPEVEK; ISSN: 1055-7903
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pyrogenic toxin (PT) family is composed of the staphylococcal enterotoxins (SE), the toxic shock syndrome toxin, and the streptococcal pyrogenic exotoxins (SPE). Whereas considerable effort has focused on characterization of PTs due to their unique biol. properties, the understanding of the evolution of this gene family is incomplete. Phylogenetic relationships for members of the PT family were estd. by examg. the previously reported nucleotide sequences of the genes encoding SPEA, SPEC, SEA, SEB, SEC1, SEC2, SEC3, SED, and SEE. Addnl., the authors present and analyze sequence data on seven previously unreported sec genes. Within the PT family, sequence divergence was partitioned in a hierarchical fashion such that mean sequence divergence ranged from 1.179 among all 16 toxin genes, 0.443 among those restricted to Staphylococcus, and 0.028 among the genes encoding 10 variants of Type C SE. Results of this study are interpreted as suggesting that the PT family consists of two large clades. One clade consists of the staphylococcal toxins SEA, SEE, and SED, being closely related to the **streptococcal** toxin **SPEC**, whereas the other clade depicts close relationships of the staphylococcal toxins SEC and SEB with the **streptococcal** toxin SPEA.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1989:451311 CAPLUS
DOCUMENT NUMBER: 111:51311
TITLE: Bacteriophage association of **streptococcal** pyrogenic **exotoxin** type **C**
AUTHOR(S): Goshorn, Stephen C.; Schlievert, Patrick M.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: J. Bacteriol. (1989), 171(6), 3068-73
CODEN: JOBAAY; ISSN: 0021-9193
DOCUMENT TYPE: Journal
LANGUAGE: English

Searcher : Shears 308-4994

AB A gene encoding **streptococcal** pyrogenic **exotoxin** type **C** (**SPE C**) was isolated from phage DNA derived from **Streptococcus** pyogenes CS112. The gene, designated speC2, was shown to reside near the phage attachment site of phage CS112. A restriction endonuclease map of the CS112 phage was generated, and the location and orientation of the speC2 gene were detd. Hybridization analyses of eight SPE C-producing strains revealed restriction fragment length **polymorphism** of the speC gene-contg. DNA fragments and further showed that each speC was linked to a common CS112 phage-derived DNA fragment.

=> d his l7-; d 1-12 ibib abs

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE' ENTERED AT 14:05:50 ON 24 SEP 1999)

L7 34 S L6

L8 12 DUP REM L7 (22 DUPLICATES REMOVED)

L8 ANSWER 1 OF 12 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 1999296572 MEDLINE

DOCUMENT NUMBER: 99296572

TITLE: A response regulator that represses transcription of several virulence operons in the group A streptococcus.

AUTHOR: Federle M J; McIver K S; Scott J R

CORPORATE SOURCE: Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.

CONTRACT NUMBER: R37-AI20723 (NIAID)
AI09460 (NIAID)

SOURCE: JOURNAL OF BACTERIOLOGY, (1999 Jun) 181 (12) 3649-57. Journal code: HH3. ISSN: 0021-9193.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199909

ENTRY WEEK: 19990903

AB A search for homologs of the Bacillus subtilis PhoP response regulator in the group A **streptococcus** (GAS) genome revealed three good candidates. Inactivation of one of these, recently identified as csrR (J. C. Levin and M. R. Wessels, Mol. Microbiol. 30:209-219, 1998), caused the strain to produce mucoid colonies and to increase transcription of hasA, the first gene in the operon for capsule synthesis. We report here that a nonpolar insertion in this gene also increased transcription of ska (encoding streptokinase), sagA (streptolysin S), and speMF (mitogenic factor) but did not affect transcription of slo (streptolysin O), mga

(multiple gene regulator of GAS), emm (M protein), scpA (complement C5a peptidase), or speB or **speC** (pyrogenic exotoxins B and C). The amounts of streptokinase, streptolysin S, and capsule paralleled the levels of transcription of their genes in all cases. Because CsrR represses genes unrelated to those for capsule synthesis, and because CsrA-CsrB is a global regulatory system in Escherichia coli whose mechanism is unrelated to that of these genes in GAS, the locus has been renamed covR, for "control of virulence genes" in GAS. Transcription of the covR operon was also increased in the nonpolar insertion **mutant**, indicating that CovR represses its own synthesis as well. All phenotypes of the covR nonpolar insertion **mutant** were complemented by the covR gene on a plasmid. CovR acts on operons expressed both in exponential and in stationary phase, demonstrating that the CovR-CovS pathway is separate from growth phase-dependent regulation in GAS. Therefore, CovR is the first multiple-gene repressor of virulence factors described for this important human pathogen.

L8 ANSWER 2 OF 12 TOXLINE
ACCESSION NUMBER: 1999:51995 TOXLINE
DOCUMENT NUMBER: CRISP-99-HL37260-12
TITLE: PATHOGENESIS AND ETIOLOGY OF KAWASAKI SYNDROME.
AUTHOR: LEUNG D Y
CORPORATE SOURCE: NATIONAL JEWISH MED & RES CTR, 1400 JACKSON STREET, DENVER, CO 80206
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R37HL37260-12
SOURCE: (1998). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199904

AB RPROJ/CRISP Kawasaki syndrome (KS) is currently the most common cause of acquired heart disease in children. Early treatment of KS with intravenous gammaglobulin significantly reduces, but does not eradicate, the occurrence of cardiovascular complications. Thus, discovery of the etiology and pathogenesis of KS is of critical importance. The current proposal will expand upon preliminary data from our lab that suggests the marked immune activation associated with acute KS is caused by a superantigen(s), e.g., a variant staphylococcal toxic shock syndrome toxin (TSST-KS) or **streptococcal** pyrogenic **exotoxin C** (**SPEC**) that activates macrophages and induces the selective stimulation of T cells bearing Vbeta2 gene segments. The specific aims will be: First, to assess the role of antibody repertoire as a

risk factor for KS. We will assay anti-toxin antibody levels in sera from acute vs convalescent KS patients, their family members and age-matched controls by using both functional assays of toxin neutralization and ELISA. We postulate that the selective deficiency of antibodies against TSST-KS and/or **SPEC** predispose to acute KS> Second, to correlate the isolation of toxin-producing bacteria with various established parameters of immune activation in acute KS. The demonstration that isolation of toxin secreting S. aureus is accompanied by the activation of macrophages and Vbeta2+ T cells will strengthen the argument that superantigens play a role in the pathogenesis of KS. Third, to determine whether the selective stimulation of T cells in patients with KS, complicated by the development of coronary artery disease, is oligoclonal or diverse, we will clone and sequence their T Cell Receptor Vbeta2 and control Vbeta gene transcripts amplified PCR. Fourth, to determine whether TSST-KS has different immunologic properties than staphylococcal TSST1 when tested on T cells, B cells, and/or vascular endothelial cells. We postulate that as the result of several critical **mutations** between variant TSST-KS vs staphylococcal TSST1, the cause of Toxic Shock Syndrome (TSS), that TSST-KS may exhibit different immunologic properties which account for at least some of the differences in the immunologic features distinguishing acute KS vs TSS. The importance of our proposed studies is that it should contribute directly to an understanding of the pathogenesis and etiology of KS. The elucidation of immune mechanisms underlying this disease will have important implications for the development of more effective therapeutic approaches to the treatment of KS as well as other diseases where similar pathologic mechanisms may exist. Furthermore, identification of the causative agent and unique populations of T cells associated with KS may allow us to more readily diagnose this disease and institute early therapy to prevent heart disease.

L8 ANSWER 3 OF 12 TOXLINE
ACCESSION NUMBER: 1999:51994 TOXLINE
DOCUMENT NUMBER: CRISP-99-HL36611-11
TITLE: CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR: SCHLIEVERT P M
CORPORATE SOURCE: UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R01HL36611-11
SOURCE: (1998). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)

FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199904

AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic toxin superantigens, notably **streptococcal** pyrogenic exotoxins (SPEs, scarlet fever toxins), in causing both acute toxic shock syndrome and vascular illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome toxin-1, with the intent to clarify the molecular mechanism(s) of action of the toxins and develop toxoid vaccines against the toxins. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient toxins for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic toxin superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR **mutagenesis**. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of **mutants**. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L8 ANSWER 4 OF 12 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-08443 BIOTECHDS
TITLE: **Mutant** non-lethal **Streptococcus** pyrogenic **exotoxin** type-**C**; and plasmid pUMN521 expression in Escherichia coli for vaccine generation and toxic shock syndrome therapy
AUTHOR: Schlievert P M; Ohlendorf D; Mitchell D T; Gahr P J
PATENT ASSIGNEE: Univ.Minnesota
LOCATION: Minneapolis, MN, USA.

PATENT INFO: WO 9824910 11 Jun 1998
APPLICATION INFO: WO 1997-US22125 5 Dec 1997
PRIORITY INFO: US 1996-33251 6 Dec 1996
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1998-333329 [29]
AN 1998-08443 BIOTECHDS
AB A **mutant Streptococcus** sp. pyrogenic exotoxin type-C (**SPE-C**) toxin (or fragment) having at least one amino acid change is new and is non-lethal compared to the wild-type. Also claimed are: vaccines containing the **mutant** toxin for protecting animals against at least one biological activity of wild-type **SPE-C**; DNA encoding the **mutant** toxin; and stably transformed (plasmid pUMN521) host cells (e.g. Escherichia coli) containing the DNA. **Mutant** toxins with substitutions (tyrosine-15 and asparagine-38 to alanine and tyrosine-17 and asparagine-38 to alanine) are specifically claimed. The **mutant** toxin preferably contains 1-6 amino acid substitutions, at least one positioned in a beta-barrel of a B-subunit, N-terminal alpha helix, diagonal alpha-helix or surface groove between subunits A and B. The above may be used to ameliorate **streptococcal** toxic shock syndrome. (55pp)

L8 ANSWER 5 OF 12 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998427177 MEDLINE
DOCUMENT NUMBER: 98427177
TITLE: **Mutational** analysis of superantigen activity responsible for the induction of skin erythema by **streptococcal** pyrogenic **exotoxin C**.
AUTHOR: Yamaoka J; Nakamura E; Takeda Y; Imamura S; Minato N
CORPORATE SOURCE: Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
SOURCE: INFECTION AND IMMUNITY, (1998 Oct) 66 (10) 5020-6. Journal code: GO7. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199901
ENTRY WEEK: 19990104
AB **Streptococcal** pyrogenic **exotoxin C** (**SPEC**), when injected intradermally, induces erythema in unsensitized rabbits. In the present study, we examined whether this erythema induction is due to the T-cell stimulatory activity of **SPEC** as a superantigen. Analysis by using single-residue **mutant SPECs** indicated that **mutant SPECs** Y15I, A16E, and Y17I, in which tyrosine 15, alanine

16, and tyrosine 17 were replaced with isoleucine, glutamic acid, and isoleucine, respectively, exhibited significantly reduced mitogenic activity for Vbeta2(+) human T cells in vitro, and Y15I showed as much as a 1, 000-fold reduction. Y15I **mutant** **SPEC**, however, retained the ability to bind to major histocompatibility complex class II antigen and to form a homodimer, implying that residue 15 is critically important for the interaction of **SPEC** with T-cell antigen receptor beta chains. When injected intradermally into normal rabbits, wild-type **SPEC** induced a characteristic erythema after 3 h in a dose-dependent fashion, which was associated with **polymorphonuclear** and mononuclear cell infiltration. This erythema formation was found to be severely suppressed by systemic pretreatment with cyclosporin A, suggesting the involvement of host T cells. Y15I **mutant** **SPEC** exhibited nearly 1, 000-fold less erythema induction in vivo than wild-type **SPEC**. Altogether, the present results strongly suggest that erythema induction in rabbits by **SPEC** is attributable mostly to its T-cell stimulatory activity as a superantigen.

L8 ANSWER 6 OF 12 TOXLINE
ACCESSION NUMBER: 1998:60284 TOXLINE
DOCUMENT NUMBER: CRISP-98-HL37260-11
TITLE: PATHOGENESIS AND ETIOLOGY OF KAWASAKI SYNDROME.
AUTHOR: LEUNG D Y
CORPORATE SOURCE: NATIONAL JEWISH CENTER, 1400 JACKSON STREET, DENVER, CO 80206
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R37HL37260-11
SOURCE: (1997). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199805
AB RPROJ/CRISP Kawasaki syndrome (KS) is currently the most common cause of acquired heart disease in children. Early treatment of KS with intravenous gammaglobulin significantly reduces, but does not eradicate, the occurrence of cardiovascular complications. Thus, discovery of the etiology and pathogenesis of KS is of critical importance. The current proposal will expand upon preliminary data from our lab that suggests the marked immune activation associated with acute KS is caused by a superantigen(s), e.g., a variant staphylococcal toxic shock syndrome toxin (TSST-KS) or **streptococcal** pyrogenic **exotoxin C** (**SPEC**) that activates macrophages and induces the selective

stimulation of T cells bearing Vbeta2 gene segments. The specific aims will be: First, to assess the role of antibody repertoire as a risk factor for KS. We will assay anti-toxin antibody levels in sera from acute vs convalescent KS patients, their family members and age-matched controls by using both functional assays of toxin neutralization and ELISA. We postulate that the selective deficiency of antibodies against TSST-KS and/or **SPEC** predispose to acute KS> Second, to correlate the isolation of toxin-producing bacteria with various established parameters of immune activation in acute KS. The demonstration that isolation of toxin secreting S. aureus is accompanied by the activation of macrophages and Vbeta2+ T cells will strengthen the argument that superantigens play a role in the pathogenesis of KS. Third, to determine whether the selective stimulation of T cells in patients with KS, complicated by the development of coronary artery disease, is oligoclonal or diverse, we will clone and sequence their T Cell Receptor Vbeta2 and control Vbeta gene transcripts amplified PCR. Fourth, to determine whether TSST-KS has different immunologic properties than staphylococcal TSST1 when tested on T cells, B cells, and/or vascular endothelial cells. We postulate that as the result of several critical **mutations** between variant TSST-KS vs staphylococcal TSST1, the cause of Toxic Shock Syndrome (TSS), that TSST-KS may exhibit different immunologic properties which account for at least some of the differences in the immunologic features distinguishing acute KS vs TSS. The importance of our proposed studies is that it should contribute directly to an understanding of the pathogenesis and etiology of KS. The elucidation of immune mechanisms underlying this disease will have important implications for the development of more effective therapeutic approaches to the treatment of KS as well as other diseases where similar pathologic mechanisms may exist. Furthermore, identification of the causative agent and unique populations of T cells associated with KS may allow us to more readily diagnose this disease and institute early therapy to prevent heart disease.

L8 ANSWER 7 OF 12 TOXLINE
ACCESSION NUMBER: 1998:60283 TOXLINE
DOCUMENT NUMBER: CRISP-98-HL36611-10
TITLE: CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR: SCHLIEVERT P M
CORPORATE SOURCE: UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 2R01HL36611-10
SOURCE: (1997). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
Searcher : Shears 308-4994

PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199805

AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic toxin superantigens, notably **streptococcal** pyrogenic exotoxins (SPEs, scarlet fever toxins), in causing both acute toxic shock syndrome and vascular illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome toxin-1, with the intent to clarify the molecular mechanism(s) of action of the toxins and develop toxoid vaccines against the toxins. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient toxins for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic toxin superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR **mutagenesis**. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of **mutants**. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L8 ANSWER 8 OF 12 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 97397661 MEDLINE
DOCUMENT NUMBER: 97397661
TITLE: Outbreak of scarlet fever at a hospital day care centre: analysis of strain relatedness with phenotypic and genotypic characteristics.
AUTHOR: Hsueh P R; Teng L J; Lee P I; Yang P C; Huang L M; Chang S C; Lee C Y; Luh K T

Searcher : Shears 308-4994

CORPORATE SOURCE: Department of Laboratory Medicine, National Taiwan University Hospital, Taipei.
SOURCE: JOURNAL OF HOSPITAL INFECTION, (1997 Jul) 36 (3) 191-200.
Journal code: ID6. ISSN: 0195-6701.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY WEEK: 19971103
AB An outbreak of scarlet fever involving 12 children occurred at a hospital day care centre from February to March 1996. Twenty-five throat isolates of **Streptococcus** pyogenes (GAS, group A **streptococcus**) available from 24 children, including 10 children with scarlet fever and 14 asymptomatic carriers, and one asymptomatic staff member were studied for the presence of genes encoding **streptococcal** pyrogenic exotoxin types A (speA), B (speB), and C (**speC**) and for protease activity. Antimicrobial susceptibilities using the E-test, cluster analysis by cellular fatty acid composition and random amplified **polymorphic** DNA (RAPD) patterns by means of arbitrarily-primed polymerase chain reaction (APPCR) of the isolates were performed to investigate the outbreak. Only one isolate from an asymptomatic child possessed the speA gene. All isolates possessed the speB gene and 24 (96%) isolates were positive for the **speC** gene. There was no difference in protease activity between isolates from children with scarlet fever and from asymptomatic carriers. Thirteen isolates (10 recovered from children with scarlet fever, two from asymptomatic children, and one from the staff member) were considered to be the same strain according to the identical antimicrobial susceptibility profile and RAPD patterns and were also considered to be similar by cluster analysis of fatty acid composition. These findings suggest that the outbreak was caused by a unique clone of GAS. We conclude that RAPD typing and cluster analysis by cellular fatty acids composition both provide a powerful tool for epidemiological investigation of GAS infections.

L8 ANSWER 9 OF 12 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 96183627 MEDLINE
DOCUMENT NUMBER: 96183627
TITLE: Genetic and phenotypic diversity among isolates of Streptococcus pyogenes from invasive infections.
AUTHOR: Chaussee M S; Liu J; Stevens D L; Ferretti J J
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, USA.
CONTRACT NUMBER: AI-19304 (NIAID)
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1996 Apr) 173 (4)

901-8.
Journal code: IH3. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199607
AB To determine if recent cases of invasive group A **streptococcal** disease were caused by strains with a unique characteristic, 117 isolates **Streptococcus** pyogenes from patients with a variety of diseases, including necrotizing fasciitis and toxic shock syndrome, were analyzed. Significant genomic heterogeneity was observed among selected isolates, as determined using pulsed-field gel electrophoresis. The frequency of the bacteriophage-associated **streptococcal** erythrogenic toxin genes A and C (speA and **speC**) among the isolates was 44% (49/112) and 34% (38/112), respectively. Forty-three percent of speA-positive isolates produced **streptococcal** erythrogenic toxin (SPE) A in vitro. Seventy-six percent (85/112) of isolates produced SPE B in vitro, and in contrast to SPE A, little variation in the concentration of SPE B in broth culture supernatants was detected. The genetic and phenotypic heterogeneity observed among isolates from recent cases of severe infection does not support a clonal basis for the resurgence of invasive **streptococcal** infections.

L8 ANSWER 10 OF 12 TOXLINE
ACCESSION NUMBER: 1996:3920 TOXLINE
DOCUMENT NUMBER: CRISP-96-HL37260-09
TITLE: PATHOGENESIS AND ETIOLOGY OF KAWASAKI SYNDROME.
AUTHOR: LEUNG D Y
CORPORATE SOURCE: NATIONAL JEWISH CENTER, 1400 JACKSON STREET, DENVER, CO 80206
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 2R37HL37260-09
SOURCE: (1995). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199604
AB RPROJ/CRISP Kawasaki syndrome (KS) is currently the most common cause of acquired heart disease in children. Early treatment of KS with intravenous gammaglobulin significantly reduces, but does not eradicate, the occurrence of cardiovascular complications. Thus, discovery of the etiology and pathogenesis of KS is of critical

importance. The current proposal will expand upon preliminary data from our lab that suggests the marked immune activation associated with acute KS is caused by a superantigen(s), e.g., a variant staphylococcal toxic shock syndrome toxin (TSST-KS) or **streptococcal** pyrogenic **exotoxin C** (**SPEC**) that activates macrophages and induces the selective stimulation of T cells bearing Vbeta2 gene segments. The specific aims will be: First, to assess the role of antibody repertoire as a risk factor for KS. We will assay anti-toxin antibody levels in sera from acute vs convalescent KS patients, their family members and age-matched controls by using both functional assays of toxin neutralization and ELISA. We postulate that the selective deficiency of antibodies against TSST-KS and/or **SPEC** predispose to acute KS> Second, to correlate the isolation of toxin-producing bacteria with various established parameters of immune activation in acute KS. The demonstration that isolation of toxin secreting S. aureus is accompanied by the activation of macrophages and Vbeta2+ T cells will strengthen the argument that superantigens play a role in the pathogenesis of KS. Third, to determine whether the selective stimulation of T cells in patients with KS, complicated by the development of coronary artery disease, is oligoclonal or diverse, we will clone and sequence their T Cell Receptor Vbeta2 and control Vbeta gene transcripts amplified PCR. Fourth, to determine whether TSST-KS has different immunologic properties than staphylococcal TSST1 when tested on T cells, B cells, and/or vascular endothelial cells. We postulate that as the result of several critical **mutations** between variant TSST-KS vs staphylococcal TSST1, the cause of Toxic Shock Syndrome (TSS), that TSST-KS may exhibit different immunologic properties which account for at least some of the differences in the immunologic features distinguishing acute KS vs TSS. The importance of our proposed studies is that it should contribute directly to an understanding of the pathogenesis and etiology of KS. The elucidation of immune mechanisms underlying this disease will have important implications for the development of more effective therapeutic approaches to the treatment of KS as well as other diseases where similar pathologic mechanisms may exist. Furthermore, identification of the causative agent and unique populations of T cells associated with KS may allow us to more readily diagnose this disease and institute early therapy to prevent heart disease.

L8 ANSWER 11 OF 12 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 93018037 MEDLINE
DOCUMENT NUMBER: 93018037
TITLE: Genetic diversity in T1M1 group A streptococci in relation to clinical outcome of infection.
AUTHOR: Norgren M; Norrby A; Holm S E
CORPORATE SOURCE: Department of Clinical Bacteriology, University of

Umea, Sweden..
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1992 Nov) 166 (5) 1014-20.
Journal code: IH3. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199301

AB Genetic diversity was found at high frequency downstream of the emm1 gene among T1M1 group A **streptococci** (GAS) isolated in Scandinavia during a recent epidemic. Clonal variation was also seen in the speA and speB genes but at much lower frequency; no variation was detected in the **speC** gene. Erythrogenic toxin A was found to be expressed at low levels in all strains; erythrogenic toxins B and C were produced in high amounts. All strains were found to harbor the speA, speB, and **speC** genes, regardless of the amount of toxin produced. No correlation was found between one specific T1M1 clone and the more serious infections when isolates from bacteremic patients (fatalities or survivors), those with uncomplicated infections, and healthy carriers were compared. Similar results were obtained in a family study in which 3 family members were found to be asymptomatic carriers of the same GAS T1M1 clone as in the bacteremic patient, defined by genotypic and phenotypic experiments.

L8 ANSWER 12 OF 12 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 89255063 MEDLINE
DOCUMENT NUMBER: 89255063
TITLE: Bacteriophage association of **streptococcal** pyrogenic **exotoxin** type **C**.
AUTHOR: Goshorn S C; Schlievert P M
CORPORATE SOURCE: Department of Microbiology, Medical School, University of Minnesota, Minneapolis 55455.
CONTRACT NUMBER: HL36611 (NHLBI)
5T32 CA09138 (NCI)
SOURCE: JOURNAL OF BACTERIOLOGY, (1989 Jun) 171 (6) 3068-73.
Journal code: HH3. ISSN: 0021-9193.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198909

AB A gene encoding **streptococcal** pyrogenic **exotoxin** type **C** (**SPE C**) was isolated from bacteriophage DNA derived from **Streptococcus** pyogenes CS112. The gene, designated speC2, was shown to reside near the phage attachment site of phage CS112. A restriction endonuclease map of the CS112 phage was generated, and the location and orientation

of the speC2 gene were determined. Hybridization analyses of eight **SPE C**-producing strains revealed restriction fragment length **polymorphism** of the **speC** gene-containing DNA fragments and further showed that each **speC** was linked to a common CS112 phage-derived DNA fragment.

=> d his l9-; d 1-44 ibib abs

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE' ENTERED AT 14:11:08 ON 24 SEP 1999)

- Author(s)

```
L9          1488 S SCHLIEVERT P?/AU
L10          596 S OHLENDORF D?/AU
L11        10364 S MITCHELL D?/AU
L12           35 S GAHR P?/AU
L13            3 S L9 AND L10 AND L11 AND L12
L14          155 S L9 AND (L10 OR L11 OR L12)
L15           48 S L10 AND (L11 OR L12)
L16            3 S L11 AND L12
L17        12277 S L9 OR L10 OR L11 OR L12
L18          174 S (L14 OR L15 OR L17) AND (L2 OR L3)
L19          174 S L13 OR L16 OR L18
L20           44 DUP REM L19 (130 DUPLICATES REMOVED)

L20  ANSWER 1 OF 44  TOXLINE
ACCESSION NUMBER:    1999:51994  TOXLINE
DOCUMENT NUMBER:     CRISP-99-HL36611-11
TITLE:               CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR:              SCHLIEVERT P M
CORPORATE SOURCE:    UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196
                     UMH, MINNEAPOLIS, MN  55455-0312
                     U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC
                     HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL
                     HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER:     5R01HL36611-11
SOURCE:              (1998). Crisp Data Base National Institutes Of
                     Health. Award Type: G = Grant
PUB. COUNTRY:        United States
DOCUMENT TYPE:       (RESEARCH)
FILE SEGMENT:        CRISP
LANGUAGE:            English
ENTRY MONTH:         199904
AB   RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract):
     The long term goals of this project are two fold:  a) to evaluate
     the role of pyrogenic toxin superantigens, notably
     streptococcal pyrogenic exotoxins (SPEs, scarlet fever
     toxins), in causing both acute toxic shock syndrome and vascular
     illnesses and chronic autoimmune and allergic diseases, and b) to
```

analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome toxin-1, with the intent to clarify the molecular mechanism(s) of action of the toxins and develop toxoid vaccines against the toxins. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient toxins for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic toxin superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR mutagenesis. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of mutants. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L20 ANSWER 2 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 1
ACCESSION NUMBER: 1998:398420 CAPLUS
DOCUMENT NUMBER: 129:53355
TITLE: Mutants of streptococcal toxin C and use as vaccines
INVENTOR(S): **Schlievert, Patrick M.; Ohlendorf, Douglas; Mitchell, David T.; Gahr, Pamala J.**
PATENT ASSIGNEE(S): Regents of the University of Minnesota, USA; Schlievert, Patrick M.; Ohlendorf, Douglas; Mitchell, David T.; Gahr, Pamala J.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9824910	A2	19980611	WO 1997-US22125	19971205
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9876256	A1	19980629	AU 1998-76256	19971205
PRIORITY APPLN. INFO.:			US 1996-33251	19961206
			WO 1997-US22125	19971205

AB This invention is directed to mutants of **Streptococcus** pyrogenes **exotoxin** type **C** (**SPE-C**) or fragments thereof, vaccine and pharmaceutical compns., and methods of using the vaccine and pharmaceutical compns. The preferred SPE-C toxin has at least one amino acid change and is substantially non-lethal compared with the wild type SPE-C toxin. The mutant SPE-C toxins can form vaccine compns. useful to protect animals against the biol. activities of wild type SPE-C toxin. Single and double substitution mutants of SPE-C were prepd. with E. coli. Rabbits immunized with these recombinant toxins were protected from challenge by S. pyogenes.

L20 ANSWER 3 OF 44 TOXLINE
ACCESSION NUMBER: 1998:60283 TOXLINE
DOCUMENT NUMBER: CRISP-98-HL36611-10
TITLE: CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR: **SCHLIEVERT P M**
CORPORATE SOURCE: UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 2R01HL36611-10
SOURCE: (1997). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199805
AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic toxin superantigens, notably **streptococcal** pyrogenic exotoxins (SPEs, scarlet fever toxins), in causing both acute toxic shock syndrome and vascular

illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome toxin-1, with the intent to clarify the molecular mechanism(s) of action of the toxins and develop toxoid vaccines against the toxins. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient toxins for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic toxin superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR mutagenesis. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of mutants. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L20 ANSWER 4 OF 44 TOXLIT
ACCESSION NUMBER: 1997:147971 TOXLIT
DOCUMENT NUMBER: CA-127-273901G
TITLE: Molecular genetics, structure, and immunobiology of **streptococcal** pyrogenic **exotoxins** A and **C**.
AUTHOR: Kim MH; **Schlievert PM**
CORPORATE SOURCE: Univ. Minnesota Medical School, Minneapolis
SOURCE: Superantigens, (1997). pp. 257-279.
CODEN: 65BEA.
PUB. COUNTRY: United States
DOCUMENT TYPE: Book; (MONOGRAPH)
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 127:273901
ENTRY MONTH: 199711

L20 ANSWER 5 OF 44 MEDLINE DUPLICATE 2

Searcher : Shears 308-4994

ACCESSION NUMBER: 97428076 MEDLINE
DOCUMENT NUMBER: 97428076
TITLE: Association of toxic shock syndrome toxin-secreting and exfoliative toxin-secreting Staphylococcus aureus with Kawasaki syndrome complicated by coronary artery disease [see comments].
COMMENT: Comment in: Pediatr Res 1998 Feb;43(2):291-3
AUTHOR: Leung D Y; Sullivan K E; Brown-Whitehorn T F; Fehringer A P; Allen S; Finkel T H; Washington R L; Makida R; **Schlievert P M**
CORPORATE SOURCE: Division of Pediatric Allergy-Immunology, The National Jewish Medical and Research Center, Denver, Colorado 80206, USA.
CONTRACT NUMBER: AR41256 (NIAMS)
HL36611 (NHLBI)
HL37260 (NHLBI)
SOURCE: PEDIATRIC RESEARCH, (1997 Sep) 42 (3) 268-72.
Journal code: OWL. ISSN: 0031-3998.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
AB Kawasaki syndrome (KS) has been reported to be associated with selective expansion of Vbeta2+ T cells and either staphylococcal toxic shock syndrome toxin-1 or **streptococcal** pyrogenic **exotoxin C** in uncomplicated cases. However, there have been no previous studies on the role of superantigens in KS associated with coronary artery disease, the major complication of this illness. The present study characterized bacteria isolated from three acute KS patients who developed coronary artery disease. Staphylococcus aureus secreting either TSST-1 (n = 3) or exfoliative toxin A (n = 1), both known to stimulate expansion of Vbeta2+ T cells, were isolated from all three patients. The percent Vbeta2+ T cells was determined in three patients with coronary artery disease. On presentation, one patient demonstrated reduction, whereas the other two showed expansion, of Vbeta2+ T cells. Repeat analyses of the latter two children showed their percent Vbeta2+ T cells to decrease toward normal. These observations suggest that coronary artery disease in KS may result from superantigenic stimulation of Vbeta2+ T cells. This is also the first demonstration of an association of staphylococcal exfoliative toxin with acute KS. The observation that three different bacterial toxins associated with KS are potent activators of Vbeta2+ T cells suggests an important role for this T cell subset in the pathogenesis of this autoimmune disease.

L20 ANSWER 6 OF 44 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:612150 CAPLUS
Searcher : Shears 308-4994

DOCUMENT NUMBER: 127:273901
TITLE: Molecular genetics, structure, and immunobiology of **streptococcal** pyrogenic **exotoxins** A and **C**
AUTHOR(S): Kim, Michael H.; **Schlievert, Patrick M.**
CORPORATE SOURCE: Univ. Minnesota Medical School, Minneapolis, MN, USA
SOURCE: Superantigens (1997), 257-279. Editor(s): **Leung, Donald Y. M.; Huber, Brigitte T.; Schlievert, Patrick M.** Dekker: New York, N. Y.
CODEN: 65BEAQ
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 75 refs.

L20 ANSWER 7 OF 44 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 97314610 EMBASE
DOCUMENT NUMBER: 1997314610
TITLE: Mitogenic factors from group G streptococci associated with scarlet fever and streptococcal toxic shock syndrome.
AUTHOR: Assimacopoulos A.P.; Stoehr J.A.; **Schlievert P.M.**
CORPORATE SOURCE: P.M. Schlievert, Univ. of Minnesota Sch. of Medicine, Department of Microbiology, Minneapolis, MN, United States
SOURCE: Advances in Experimental Medicine and Biology, (1997) 418/- (109-114).
Refs: 11
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Since 1987, over 30 group G **streptococcus** (GGS) clinical isolates have been referred our laboratory and 3 have been investigated for production of **streptococcal** pyrogenic exotoxins(SPEs) A, B, and C. One isolate was associated with scarlet fever and two others with **streptococcal** toxic shock syndromes(STSS). All three isolates were grown in culture and shown not to produce SPEs A, B, and C by double immunodiffusion and Western blotting of ethanol precipitated, concentrated culture fluid. Isolated DNA from these organisms, separated by agarose gel electrophoresis, blotted on nylon membranes and developed with a digoxigenin detection system, failed to hybridize with probes specific for the genes speA, speB, and **speC**. We next

investigated these isolates for the production of antigenically distinct mitogens by subjecting ammonium sulfate or ethanol precipitated culture fluids to isoelectric focusing(IEF) and assaying fractions from IEF for mitogenicity by use of a rabbit splenocyte proliferation assay. All three isolates showed three peaks of mitogenic activity. The two largest peaks of mitogenic activity from one isolate were assayed for pyrogenicity and the ability to enhance lethal lipopolysaccharide (LPS) shock in a rabbit model. After injection of the sample, rabbits were observed for 4 hours and then given a sub-lethal injections of LPS. All the rabbits exhibited fever but none died. In an earlier experiment, all rabbits exhibited fever and 2/3 died. These results indicate that GGS produce mitogenic factors which are distinct from SPEs A, B, and C and could be novel superantigens.

L20 ANSWER 8 OF 44 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:50671 CAPLUS
DOCUMENT NUMBER: 124:137848
TITLE: Nucleic acid coding for toxin associated with Kawasaki syndrome
INVENTOR(S): Leung, Donald; **Schlievert, Patrick**; Meissner, Cody; Fulton, David
PATENT ASSIGNEE(S): University of Minnesota, USA; New England Medical Center Hospital, Inc.; National Jewish Center for Immunology and Respiratory Medicine
SOURCE: U.S., 9 pp. Cont.-in-part of U.S. Ser. No. 42, 731.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5476767	A	19951219	US 1993-152456	19931112
US 5470716	A	19951128	US 1993-42731	19930405
WO 9422895	A1	19941013	WO 1994-US3524	19940330
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9466232	A1	19941024	AU 1994-66232	19940330
WO 9520648	A1	19950803	WO 1995-US1237	19950130
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR,				

NE, SN, TD, TG

AU 9517373	A1	19950815	AU 1995-17373	19950130
US 5585465	A	19961217	US 1995-440221	19950512
PRIORITY APPLN. INFO.:			US 1993-42731	19930405
			US 1993-152456	19931112
			US 1994-190653	19940128
			WO 1994-US3524	19940330
			WO 1995-US1237	19950130

AB Nucleic acid mols. coding for toxins assocd. with Kawasaki syndrome were isolated and characterized. Also described are various applications of the nucleic acid mols. Thus, cultures taken from Kawasaki syndrome patients exhibited (1) the presence of toxic shock syndrome toxin (TSST), (2) the presence of white, TSST-producing Staphylococcus aureus in the culture, (3) **Streptococcus exotoxin** B or **C**, or (4) Streptococcus which produces either of these strepexotoxins. The gene coding for TSST assocd. with Kawasaki syndrome was isolated and sequenced. The gene sequence differed from related sequences for TSST-1 and ovine-TSST at positions 326, 359, 360, 363, and 381. It codes for a protein toxin of 234 amino acids. These sequence differences provide a methodol. for screening for Staphylococcus aureus assocd. with Kawasaki syndrome with sequence-specific amplification primers.

L20 ANSWER 9 OF 44 TOXLIT

ACCESSION NUMBER:	1996:57919 TOXLIT
DOCUMENT NUMBER:	CA-124-137848F
TITLE:	Nucleic acid coding for toxin associated with Kawasaki syndrome.
AUTHOR:	Leung D; **Schlievert P**; Meissner C; Fulton D
SOURCE:	(1995). U.S. PATENT NO. 5476767 12/19/95 (University of Minnesota).
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Patent
FILE SEGMENT:	CA
LANGUAGE:	English
OTHER SOURCE:	CA 124:137848
ENTRY MONTH:	199605

AB Nucleic acid mols. coding for toxins assocd. with Kawasaki syndrome were isolated and characterized. Also described are various applications of the nucleic acid mols. Thus, cultures taken from Kawasaki syndrome patients exhibited (1) the presence of toxic shock syndrome toxin (TSST), (2) the presence of white, TSST-producing Staphylococcus aureus in the culture, (3) **Streptococcus exotoxin** B or **C**, or (4) Streptococcus which produces either of these strepexotoxins. The gene coding for TSST assocd. with Kawasaki syndrome was isolated and sequenced. The gene sequence differed from related sequences for TSST-1 and ovine-TSST at positions 326, 359, 360, 363, and 381. It codes for a protein toxin of 234 amino acids. These sequence differences provide a

methodol. for screening for Staphylococcus aureus assocd. with Kawasaki syndrome with sequence-specific amplification primers.

L20 ANSWER 10 OF 44 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 4
ACCESSION NUMBER: 1996:22248 BIOSIS
DOCUMENT NUMBER: PREV199698594383
TITLE: Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis.
AUTHOR(S): Leung, Donald Y. M. (1); Travers, Jeffrey B.; Giorno, Ralph; Norris, David A.; Skinner, Robert; Aelion, Jacob; Kazemi, Leslie V.; Kim, Michael H.; E., Anne; Trumble; Kotb, Malak; **Schlievert, Patrick M.**
CORPORATE SOURCE: (1) Dep. Pediatrics, National Jewish Center Immunol. Respiratory Med., 1400 Jackson St., Denver, CO 80206 USA
SOURCE: Journal of Clinical Investigation, (1995) Vol. 96, No. 5, pp. 2106-2112.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Recent studies have suggested that T cells play a critical role in the pathogenesis of psoriasis. Guttate psoriasis is a well-defined form of psoriasis frequently associated with streptococcal throat infection. This study tested the hypothesis that T cells in acute guttate psoriasis skin lesions may be activated by streptococcal superantigens. Peripheral blood as well as lesional and perilesional skin biopsies were analyzed for T cell receptor V-beta repertoire using monoclonal antibodies against 10 different V-beta families. Skin biopsies from all patients with acute guttate psoriasis, but not skin biopsies from patients with acute atopic dermatitis or inflammatory skin lesions induced in normal subjects with sodium lauryl sulfate, demonstrated selective accumulation of V-beta-2+ T cells (P lt 0.05). The expansion of V-beta-2+ T cells occurred in both the CD4+ and the CD8+ T cell subsets. Sequence analysis of T cell receptor beta chain genes of V-beta-2-expressing T cells from skin biopsies of patients with guttate psoriasis showed extensive junctional region diversity that is more compatible with a superantigen rather than a conventional (nominal) antigen-driven T cell response. All streptococcal isolates from patients with guttate psoriasis secreted **streptococcal** pyrogenic **exotoxin C**, a superantigen known to stimulate marked V-beta-2+ T cell expansion. These data support the concept that acute guttate psoriasis is associated with superantigenic stimulation of T cells triggered by streptococcal superantigen(s).

L20 ANSWER 11 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 5
ACCESSION NUMBER: 1995:318314 CAPLUS
DOCUMENT NUMBER: 122:103479
TITLE: Bacterial superantigens induce T cell expression

of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen, via stimulation of interleukin 12 production

AUTHOR(S): Leung, Donald Y. M.; Gately, Maurice; Trumble, Anne; Ferguson-Darnell, Bonnie; **Schlievert, Patrick M.**; Picker, Louis J.

CORPORATE SOURCE: Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, 80206, USA

SOURCE: J. Exp. Med. (1995), 181(2), 747-53
CODEN: JEMEAV; ISSN: 0022-1007

DOCUMENT TYPE: Journal

LANGUAGE: English

AB T lymphocyte infiltration is a prominent feature of the skin inflammation assocd. with infections by toxin (superantigen)-secreting Staphylococcus aureus or Streptococcus bacteria. The cutaneous lymphocyte-assocd. antigen (CLA) has been hypothesized to be a homing receptor (HR) involved in selective migration of memory/effector T cells to the skin. Since the expression of this putative skin-selective HR is known to be under strict microenvironmental control, the authors sought to det. the effect of staphylococcal and streptococcal toxins on T cell expression of CLA. After in vitro stimulation of peripheral blood mononuclear cells with staphylococcal enterotoxin B, toxic shock syndrome toxin-1, and **streptococcal** pyrogenic **exotoxins** A and **C**, there was a significant increase in the nos. of CLA+ T cell blasts, but not blasts bearing the mucosa-assocd. adhesion mol. .alpha.e.beta.7-integrin, compared with T cells stimulated with phytohemagglutinin (PHA) or anti-CD3. Bacterial toxins were also found to specifically induce interleukin (IL) 12 prodn. More importantly, induction of toxin-induced CLA expression was blocked by anti-IL-12, and the addn. of IL-12 to PHA-stimulated T cells induced CLA, but not .alpha.e.beta.7-integrin, expression. These data suggest that bacterial toxins induce the expansion of skin-homing CLA+ T cells in an IL-12-dependent manner, and thus may contribute to the development of skin rashes in superantigen-mediated diseases.

L20 ANSWER 12 OF 44 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1996:493080 CAPLUS
DOCUMENT NUMBER: 125:162801

TITLE: Structural studies of streptococcal pyrogenic exotoxin superantigens

AUTHOR(S): Hauser, Alan R.; Vath, Gregory M.; **Ohlendorf, Douglas H.; Schlievert, Patrick M.**

CORPORATE SOURCE: Div. Infect. Dis., Univ. California, San Francisco, CA, USA

SOURCE: Bact. Superantigens (1995), 39-48. Editor(s):

Thibodeau, Jacques; Sekaly, Rafick-Pierre.
Landes: Austin, Tex.
CODEN: 63EWAD
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 40 refs. focusing on the structural relationships among the group A streptococcal pyrogenic exotoxins (streptococcal pyrogenic exotoxin type A; streptococcal pyrogenic exotoxin type B; **streptococcal** pyrogenic **exotoxin** type **C**; streptococcal superantigen, SSA; mitogenic factor); and groups B, **C**, F, and G **streptococcal** pyrogenic **exotoxins**.

L20 ANSWER 13 OF 44 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 96191582 MEDLINE
DOCUMENT NUMBER: 96191582
TITLE: The potential role of bacterial superantigens in the pathogenesis of Kawasaki syndrome.
AUTHOR: Leung D Y; Meissner C; Fulton D; **Schlievert P M**
CORPORATE SOURCE: Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206, USA.
CONTRACT NUMBER: HL37260 (NHLBI)
HL36611 (NHLBI)
AR41256 (NIAMS)
SOURCE: JOURNAL OF CLINICAL IMMUNOLOGY, (1995 Nov) 15 (6 Suppl) 11S-17S.
Journal code: HRC. ISSN: 0271-9142.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
AB Kawasaki syndrome is an acute multisystem vasculitis of infancy and early childhood associated with high fever, mucocutaneous inflammation, and the development of coronary artery abnormalities. Despite the widely held belief that Kawasaki syndrome is an infectious disease, investigations have failed to identify a causal organism. Previous studies have demonstrated that this illness is associated with marked activation of monocyte/macrophages and the selective expansion of V beta 2-, less so, of V beta 8.1/8.2-expressing T cells in the peripheral blood from Kawasaki syndrome patients during the acute phase of their illness. These immunologic features are characteristic of diseases that are caused by bacterial toxins which act as superantigens. Staphylococcal enterotoxins and streptococcal exotoxins are prototypic superantigens which stimulate large populations of T cells expressing particular T-cell receptor beta-chain variable (V beta)

gene segments. Using the V beta 2+ T-cell expansion as an "immunologic footprint" for a superantigen, we have extended these observations to the identification and isolation of a novel clone of toxic shock syndrome toxin-1-producing Staphylococcus aureus in the majority of patients with Kawasaki syndrome and streptococcal pyrogenic exotoxin B/**streptococcal** pyrogenic **exotoxin C**-producing streptococci in a minority of Kawasaki syndrome patients. Toxic shock syndrome toxin-1, streptococcal pyrogenic exotoxin B, and **streptococcal** pyrogenic **exotoxin C** are known to stimulate V beta 2+ T cells. These observations support the hypothesis that the activation of V beta 2+ T cells during the acute phase of Kawasaki syndrome is caused by bacterial superantigen(s).

L20 ANSWER 14 OF 44 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 96191581 MEDLINE
DOCUMENT NUMBER: 96191581
TITLE: Molecular structure of staphylococcus and streptococcus superantigens [published erratum appears in J Clin Immunol 1996 Mar;16(2):126].
AUTHOR: **Schlievert P M**; Bohach G A; **Ohlendorf D H**; Stauffacher C V; Leung D Y; Murray D L; Prasad G S; Earhart C A; Jablonski L M; Hoffmann M L; Chi Y I
CORPORATE SOURCE: Department of Microbiology, University of Minnesota Medical School, Minneapolis, 55455-0312, USA.
CONTRACT NUMBER: AI22159 (NIAID)
GM46436+ (NIGMS)
HL36611 (NHLBI)
SOURCE: JOURNAL OF CLINICAL IMMUNOLOGY, (1995 Nov) 15 (6 Suppl) 4S-10S.
Journal code: HRC. ISSN: 0271-9142.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
AB Staphylococcus aureus and streptococci, notably those belonging to group A, make up a large family of true exotoxins referred to as pyrogenic toxin superantigens. These toxins cause toxic shock-like syndromes and have been implicated in several allergic and autoimmune diseases. Included within this group of proteins are the staphylococcal enterotoxins, designated serotypes A, B, Cn, D, E, and G; two forms of toxic shock syndrome toxin-1 also made by Staphylococcus aureus; the group A streptococcal pyrogenic exotoxins, serotypes A, B, and C; and recently described toxins associated with groups B, C, F, and G streptococci. The nucleotide sequences of the genes for all of the toxins except those from the groups B, C, F, and G streptococcal strains have been sequenced. The

sequencing studies indicate that staphylococcal enterotoxins B and **C** and **streptococcal** pyrogenic **exotoxin** A
share highly significant sequence similarity; staphylococcal enterotoxins A, D, and E share highly significant sequence similarity; and toxic shock syndrome toxin-1 and **streptococcal** pyrogenic **exotoxin** B and **C**
share little, if any, sequence similarity with any of the toxins. Despite the dissimilarities seen in primary amino acid sequence among some members of the toxin family, it was hypothesized that there was likely to be significant three-dimensional structure similarity among all the toxins. The three-dimensional structures of three of the pyrogenic toxin superantigens have been determined recently. The structural features of two of these, toxic shock syndrome toxin-1 and enterotoxin C3, are presented. Toxic shock syndrome-1 exists as a protein with two major domains, referred to as A and B. The molecule begins with a short N-terminal alpha-helix that then leads into a clawshaped structure in domain B that is made up of beta strands.

L20 ANSWER 15 OF 44 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1994-332793 [41] WPIDS
DOC. NO. CPI: C1994-151314
TITLE: Treatment of Kawasaki syndrome - by administering an anti-staphylococcal agent on an anti-streptococcal agent, pref. penicillin or cephalosporin.
DERWENT CLASS: B02
INVENTOR(S): FULTON, D; KOTZIN, B; LEUNG, D; MEISSNER, C; **SCHLIEVERT, P**
PATENT ASSIGNEE(S): (NAJE-N) NAT JEWISH CENT IMMUNOLOGY & RESPIRATORY; (NEWE-N) NEW ENGLAND MED CENT HOSPITALS; (MINU) UNIV MINNESOTA
COUNTRY COUNT: 44
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9422443	A1	19941013	(199441)*	EN	19
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE					
W: AU BB BG BR BY CA CZ FI HU JP KP KR KZ LK MG MN MW NO NZ PL RO RU SD SK UA VN					
AU 9465536	A	19941024	(199505)		
US 5460813	A	19951024	(199548)		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9422443	A1	WO 1994-US3489	19940330

Searcher : Shears 308-4994

AU 9465536	A	AU 1994-65536	19940330
US 5460813	A	US 1993-42863	19930405

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9465536	A	Based on	WO 9422443

PRIORITY APPLN. INFO: US 1993-42863 19930405
AN 1994-332793 [41] WPIDS
AB WO 9422443 A UPAB: 19941206
Treatment of a subject suffering from Kawasaki syndrome (KS) comprises: administering an anti-staphylococcal agent or an anti-streptococcal agent to alleviate KS, with the proviso that the agent is not gamma globulin.

Also claimed, is a method for treating KS comprising administering an anti-toxin selected from an anti-toxic shock syndrome toxin (TSST) agent, an anti-**streptococcal** pyrogenic exotoxin B (SPEB) agent and an anti-**streptococcal** pyrogenic **exotoxin C** (**SPEC**) agent to alleviate KS,with the proviso that the anti-toxin is not gamma globulin.

USE - The methods can be used for treating or preventing KS.
Dwg.0/2
ABEQ US 5460813 A UPAB: 19951204
Treatment of Kawasaki syndrome comprises administration of an anti-TSST-1, (but not gamma-globulin), dispersed with the usual carriers and opt. additives. Streptococcal bacteria and its associated antigens, and Staphylococcal bacteria produce a toxic shock syndrome toxin, TSST-1, and antibodies to this toxin are diagnostic reagents and therapeutics for Kawasaki syndrome.

USE - The antibody anti-TSS-1 is a diagnostic reagent and therapeutic for Kawasaki syndrome.

ADVANTAGE - The prods. avoid the intravenous administration of gamma-globulin and the associated acquired heart disease in children.
Dwg.0/2

L20 ANSWER 16 OF 44 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 95153981 MEDLINE
DOCUMENT NUMBER: 95153981
TITLE: Dual infections with Staphylococcus aureus and Streptococcus pyogenes causing toxic shock syndrome. Possible synergistic effects of toxic shock syndrome toxin 1 and **streptococcal** pyrogenic **exotoxin C**.
AUTHOR: Smith R J; **Schlievert P M**; Himelright I M; Baddour L M
Searcher : Shears 308-4994

CORPORATE SOURCE: Department of Medicine, University of Tennessee Medical Center at Knoxville 37920-6999.
SOURCE: DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE, (1994 Aug) 19 (4) 245-7.
Journal code: DMI. ISSN: 0732-8893.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
AB We describe a 35-year-old woman with clinical, microbiologic, and serologic findings suggesting that the patient developed toxic shock syndrome as a result of dual infections caused by toxin-producing strains of Staphylococcus aureus and Streptococcus pyogenes. Certain aspects of the pathogenesis of this toxin-related syndrome are reviewed.

L20 ANSWER 17 OF 44 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 94224529 MEDLINE
DOCUMENT NUMBER: 94224529
TITLE: Apparent lower rates of streptococcal toxic shock syndrome and lower mortality in children with invasive group A streptococcal infections compared with adults.
AUTHOR: Davies H D; Matlow A; Scriver S R; **Schlievert P**; Lovgren M; Talbot J A; Low D E
CORPORATE SOURCE: Division of Infectious Diseases, Hospital for Sick Children, Toronto, Ontario, Canada..
SOURCE: PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1994 Jan) 13 (1) 49-56. Ref: 55
Journal code: OXJ. ISSN: 0891-3668.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
AB Since 1985 there have been worldwide reports of increases in severe invasive Group A **streptococcal** (IGAS) infections. We reviewed the charts of all children with IGAS infections (defined as isolation of Group A **streptococcus** from a normally sterile site) presenting to our institution over a 7-year period (January, 1985, to December, 1991) and the literature. **Streptococcal** toxic shock syndrome required hypotension and multisystem organ involvement. Twenty-four patients (mean age, 4.96 +/- 4.4 years) were identified with IGAS infection. One patient (presenting in 1989) met the criteria for probable **streptococcal** toxic shock syndrome and none died. Eight of 19 Group A

streptococcal isolates tested were **streptococcal** pyrogenic exotoxin (SPE) A producers, most (90%) had the **speC** gene and all had the speB gene and produced the toxin. No M or T type predominated. The low rates of **streptococcal** toxic shock syndrome and fatalities among children with IGAS infection are consistent with other pediatric but not with adult series. The apparent differences in outcome of IGAS between children and adults were not explained by the virulence factors we examined and may warrant further investigation.

L20 ANSWER 18 OF 44 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 94048806 MEDLINE
DOCUMENT NUMBER: 94048806
TITLE: Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome [see comments].
COMMENT: Comment in: Lancet 1994 Jan 29;343(8892):299
Comment in: Lancet 1994 Jan 29;343(8892):299-300
Comment in: Lancet 1994 Jan 29;343(8892):300
AUTHOR: Leung D Y; Meissner H C; Fulton D R; Murray D L; Kotzin B L; **Schlievert P M**
CORPORATE SOURCE: Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO 80206..
CONTRACT NUMBER: AR41256 (NIAMS)
HL36611 (NHLBI)
HL37260 (NHLBI)
+
SOURCE: LANCET, (1993 Dec 4) 342 (8884) 1385-8.
Journal code: L0S. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199402
AB Kawasaki syndrome (KS), the main cause of acquired heart disease in children, is associated with the selective expansion of V beta 2+ T cells in peripheral blood. Our study suggests that KS may be caused by a superantigen--a staphylococcal or **streptococcal** toxin. Bacteria were cultured without knowledge of their origin, from the throat, rectum, axilla, and groin of 16 patients with untreated acute KS and 15 controls. Bacteria producing toxins were isolated from 13 of 16 KS patients but from only 1 of 15 controls ($p < 0.0001$). Toxic shock syndrome toxin (TSST) secreting Staphylococcus aureus was isolated from 11 of the 13 toxin-positive cultures, and **streptococcal** pyogenic **exotoxin** (SPE) B and **C** were found in the other 2. These toxins are known to stimulate V beta 2+ T cells. All TSST-producing KS isolates were tryptophan auxotrophs indicating they were clonally related. S

aureus isolates from acute KS patients were unusual because they produced less lipase, haemolysin, and protease compared to other isolates ($p < 0.01$). S aureus colonies from KS patients were white, and could be easily mistaken for coagulase-negative staphylococci, whereas colonies of non-KS isolates were gold. These observations suggest that the expansion of V beta 2+ T cells in most patients with KS may be caused by a new clone of TSST-producing S aureus, and, in a minority of patients, SPEB-producing or **SPEC** -producing **streptococci**.

L20 ANSWER 19 OF 44 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 93320193 MEDLINE
DOCUMENT NUMBER: 93320193
TITLE: Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991.
AUTHOR: Demers B; Simor A E; Vellend H; **Schlievert P M**; Byrne S; Jamieson F; Walmsley S; Low D E
CORPORATE SOURCE: Department of Microbiology, Mount Sinai Hospital, Toronto, Ontario, Canada..
SOURCE: CLINICAL INFECTIOUS DISEASES, (1993 Jun) 16 (6) 792-800; discussion 801-2.
Journal code: A4J. ISSN: 1058-4838.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310

AB During the past few years, there has been an apparent increase in serious infections due to group A **streptococci** (GAS) worldwide. We describe our experience with severe invasive GAS infections in Ontario, Canada, during the past 5 years (February 1987 through December 1991). A case was defined as the isolation of GAS from blood or normally sterile tissue in association with hypotension (systolic blood pressure, < 90 mm Hg). Fifty cases were identified in patients ranging in age from 4 to 100 years (median age, 47 years); 29 (58%) of the patients died. A primary focus of infection was identified in 38 cases (76%), with soft tissue being the site involved most frequently (68%). No focus of infection was found in 12 patients, and 36 patients (72%) were bacteremic. Complications included acute respiratory distress syndrome (21 of 50), acute renal failure (20 of 50), hypocalcemia (19 of 24), elevated creatinine kinase values (21 of 27), coagulation abnormalities (15 of 21), and hepatitis (15 of 24). Eleven cases (22%) were nosocomial; one of these was secondary to another nosocomial case. Thirty-three isolates were available for M and T typing and for determination of the presence of the genes for **streptococcal** pyrogenic exotoxin (SPE). The most frequent types were M1T1 (10) and M12/T12 (8). Twelve isolates possessed the speA gene, and 16 isolates had the **speC** gene. Only three

isolates possessed both speA and **speC**. All isolates possessed the speB gene.

L20 ANSWER 20 OF 44 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 93281892 MEDLINE
DOCUMENT NUMBER: 93281892
TITLE: Group A streptococcal bacteremia in a mid-south children's hospital.
AUTHOR: Leggiadro R J; Bugnitz M C; Peck B A; Luedtke G S; Kim M H; Kaplan E L; **Schlievert P M**
CORPORATE SOURCE: Department of Pediatrics, University of Tennessee, Memphis..
CONTRACT NUMBER: HL 36611 (NHLBI)
SOURCE: SOUTHERN MEDICAL JOURNAL, (1993 Jun) 86 (6) 615-8. Journal code: UVH. ISSN: 0038-4348.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199309
AB We reviewed microbiology and infection control records at a Memphis children's hospital from 1982 to 1990 to obtain epidemiologic, clinical, and microbiologic data on group A **streptococcal** (GAS) bacteremia. Varicella was the underlying condition in 8 of 37 (22%) patients identified and was often associated with severe GAS disease, including toxic shock-like syndrome. Twenty-one of 31 (68%) available blood isolates made GAS pyrogenic exotoxin (SPE) B by Ouchterlony immunodiffusion; gene probes identified **speC** and speA in 18 (58%) and 8 (26%) isolates, respectively. The B/C toxin profile, identified in 11 (35%) isolates, was the most common profile in this population, and the overall rate for **speC** was higher than rates recently reported from other areas. Although the clinical significance of the toxin profiles in our population is unclear, these data emphasize the geographic and temporal variability in the microbiologic properties of GAS disease.

L20 ANSWER 21 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 13
ACCESSION NUMBER: 1993:162146 CAPLUS
DOCUMENT NUMBER: 118:162146
TITLE: Molecular population genetic evidence of horizontal spread of two alleles of the pyrogenic exotoxin C gene (**speC**) among pathogenic clones of **Streptococcus** pyogenes
AUTHOR(S): Kapur, Vivek; Nelson, Kimberlyn; **Schlievert, Patrick M.**; Selander, Robert K.; Musser, James M.
CORPORATE SOURCE: Dep. Pathol., Baylor Coll. Med., Houston, TX,

77030, USA
SOURCE: Infect. Immun. (1992), 60(9), 3513-17
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has recently been demonstrated that the bacteriophage-borne gene (**speC**) encoding pyrogenic exotoxin C is harbored by phylogenetic lineages representing virtually the entire breadth of genomic differentiation present in the species **Streptococcus** pyogenes (J. M. Musser, et al., 1991). To det. whether the speC genes occurring in assocn. with divergent chromosomal genotypes (clones) are identical or represent a group of allelic variants, the authors sequenced speC from 23 S. pyogenes strains representing 15 clones identified by multilocus enzyme electrophoresis. Two alleles of speC are present in natural populations, and each allele occurs in clones that are well differentiated in overall chromosomal character; in one case, isolates of a single clone had different speC alleles. The authors interpret these patterns of toxin allele-clone distribution as evidence of occasional episodes of speC horizontal dissemination, presumably by bacteriophage-mediated gene transfer and recombination.

L20 ANSWER 22 OF 44 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 93105954 MEDLINE
DOCUMENT NUMBER: 93105954
TITLE: First reported case of Streptococcus pyogenes infection with toxic shock-like syndrome in Italy.
AUTHOR: Cherchi G B; Kaplan E L; **Schlievert P M**; Bitti A; Orefici G
CORPORATE SOURCE: Laboratorio di Patologia Clinica, Ozieri, Italy..
SOURCE: EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES, (1992 Sep) 11 (9) 836-8.
Journal code: EM5. ISSN: 0934-9723.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303

AB A 43-year-old male who sustained a superficial hand injury developed streptococcal toxic shock-like syndrome and died within 48 hours. The clinical course of the illness in this previously well patient was rapid and fulminant. The organism responsible was a group A beta-hemolytic streptococcus which was identified as opacity factor negative, M serotype 1, T type 1. The organism produced **streptococcal** pyrogenic **exotoxins** B and **C**, but no detectable exotoxin A although it carried speA, the gene for exotoxin A. This is the first case reported in Italy, and further emphasizes the virulence of these organisms and the rapidity with which the illness can progress.

L20 ANSWER 23 OF 44 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 92112344 MEDLINE
DOCUMENT NUMBER: 92112344
TITLE: Distinct T-cell receptor V beta gene usage by human T lymphocytes stimulated with the streptococcal pyrogenic exotoxins and pep M5 protein.
AUTHOR: Tomai M A; **Schlievert P M**; Kotb M
CORPORATE SOURCE: Veteran's Administration Medical Center, Memphis, Tennessee 38104..
CONTRACT NUMBER: GM-38530 (NIGMS)
HL36611 (NHLBI)
AI 08346-01 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (1992 Feb) 60 (2) 701-5.
Journal code: GO7. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199204
AB A number of **streptococcal** products, including the **streptococcal** pyrogenic exotoxin (SPE) types A, B, and C as well as a 22-kDa fragment of M type 5 protein (pep M5), are potent stimulants of human T-lymphocyte blastogenesis and belong to the newly designated family of superantigens. The V beta usage of human T cells stimulated with these toxins was investigated by using the polymerase chain reaction. We demonstrate that SPE A, B, and C as well as pep M5 stimulate the proliferation of T cells in a dose-dependent manner. pep M5 stimulates cells bearing V beta 2, 4, and 8 elements of the T-cell receptor (TCR), whereas SPE A stimulates TCR V beta 2-, 12-, 14-, and 15-bearing cells. SPE B stimulated only cells expressing TCR V beta 8 elements, while **SPE C** stimulated cells expressing V beta 1, 2, 5.1, and 10. These studies reveal that the preferential usage of particular V beta elements is distinct for these different superantigens, which may be important in the pathogenesis of various **streptococcal** diseases.

L20 ANSWER 24 OF 44 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1992:168099 CAPLUS
DOCUMENT NUMBER: 116:168099
TITLE: Stability of streptococcal pyrogenic exotoxin production with laboratory manipulation of group A streptococci
AUTHOR(S): Kaplan, Edward L.; Johnson, Dwight R.; Wlazlo, Anthony; Kim, Michael H.; **Schlievert, Patrick M.**
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
Searcher : Shears 308-4994

SOURCE: J. Infect. Dis. (1991), 164(6), 1210-11
CODEN: JIDIAQ; ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because of reported differences in the prodn. of streptococcal pyrogenic exotoxins by group A strains assocd. with severe streptococcal infections, the stability of exotoxin prodn. by specific strains was examd. by passing group A streptococci on blood agar culture plates daily for 20 days. No changes were detected in either exotoxin genes or in exotoxin prodn. during this time, suggesting that these reported differences are due to other explanations such as differences in the strains collected from various geog. areas or to lab. methodol. differences.

L20 ANSWER 25 OF 44 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 92046774 EMBASE
DOCUMENT NUMBER: 1992046774

TITLE: Distinct T-cell receptor V.beta. gene usage by human T lymphocytes stimulated with the streptococcal pyrogenic exotoxins and pep M5 protein.

AUTHOR: Tomai M.A.; **Schlievert P.M.**; Kotb M.
CORPORATE SOURCE: Veteran's Admin. Medical Ctr.,Memphis, TN 38104, United States

SOURCE: Infection and Immunity, (1991) 60/2 (701-705).
ISSN: 0019-9567 CODEN: INFIBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A number of **streptococcal** products, including the **streptococcal** pyrogenic exotoxin (SPE) types A, B, and C as well as a 22-kDa fragment of M type 5 protein (pep M5), are potent stimulants of human T-lymphocyte blastogenesis and belong to the newly designated family of superantigens. The V.beta. usage of human T cells stimulated with these toxins was investigated by using the polymerase chain reaction. We demonstrate that SPE A, B, and C as well as pep M5 stimulate the proliferation of T cells in a dose-dependent manner. pep M5 stimulates cells bearing V.beta. 2, 4, and 8 elements of the T-cell receptor (TCR), whereas SPE A stimulates TCR V.beta. 2-, 12-, 14-, and 15-bearing cells. SPE B stimulated only cells expressing TCR V.beta. 8 elements, while **SPE C** stimulated cells expressing V.beta. 1, 2, 5.1, and 10. These studies reveal that the preferential usage of particular V.beta. elements is distinct for these different superantigens, which may be important in the pathogenesis of various **streptococcal** diseases.

L20 ANSWER 26 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 16
ACCESSION NUMBER: 1989:451311 CAPLUS
DOCUMENT NUMBER: 111:51311
TITLE: Bacteriophage association of **streptococcal** pyrogenic **exotoxin** type **C**
AUTHOR(S): Goshorn, Stephen C.; **Schlievert, Patrick M.**
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: J. Bacteriol. (1989), 171(6), 3068-73
CODEN: JOBAAY; ISSN: 0021-9193
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A gene encoding **streptococcal** pyrogenic **exotoxin** type **C** (**SPE C**) was isolated from phage DNA derived from **Streptococcus** pyogenes CS112. The gene, designated speC2, was shown to reside near the phage attachment site of phage CS112. A restriction endonuclease map of the CS112 phage was generated, and the location and orientation of the speC2 gene were detd. Hybridization analyses of eight SPE C-producing strains revealed restriction fragment length polymorphism of the speC gene-contg. DNA fragments and further showed that each speC was linked to a common CS112 phage-derived DNA fragment.

L20 ANSWER 27 OF 44 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 89359875 MEDLINE
DOCUMENT NUMBER: 89359875
TITLE: Quantification and toxicity of group A streptococcal pyrogenic exotoxins in an animal model of toxic shock syndrome-like illness.
AUTHOR: Lee P K; **Schlievert P M**
CORPORATE SOURCE: Department of Microbiology, University of Minnesota Medical School, Minneapolis 55455.
CONTRACT NUMBER: HL36611 (NHLBI)
SOURCE: JOURNAL OF CLINICAL MICROBIOLOGY, (1989 Aug) 27 (8) 1890-2.
Journal code: HSH. ISSN: 0095-1137.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
AB Toxic shock-like syndrome isolates of group A **streptococci** were evaluated for production of pyrogenic exotoxins (also called SPEs, scarlet fever toxins, and erythrogenic toxins). The isolates were consecutively obtained during 1987 and 1988. Of these isolates, 23 of 26 made SPE type A, 10 of 26 made SPE B, and 8 of 26 made **SPE C**. SPE A was produced in significantly greater

amounts than SPEs B and C (3.2 micrograms/ml of culture fluid compared with 0.7 and 0.6 microgram/ml, respectively). SPE A, administered in miniosmotic pumps implanted subcutaneously in rabbits, was significantly more toxic than **SPE C** ; seven of eight rabbits succumbed after challenge with 150 or 300 micrograms of SPE A, compared with one of six after challenge with **SPE C**.

L20 ANSWER 28 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 18
ACCESSION NUMBER: 1989:437696 CAPLUS
DOCUMENT NUMBER: 111:37696
TITLE: Group A streptococcal pyrogenic exotoxin (scarlet fever toxin) type A and blastogen A are the same protein
AUTHOR(S): **Schlievert, Patrick M.**; Gray, Ernest D.
CORPORATE SOURCE: Dep. Microbiol., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Infect. Immun. (1989), 57(6), 1865-7
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Group A **streptococcal** pyrogenic **exotoxins** A, B, and **C** (also known as scarlet fever toxins and erythrogenic toxins) were evaluated for relatedness to another streptococcus-derived lymphocyte mitogen, plastogen A. Streptococcal pyrogenic exotoxin A and blastogen A were immunol. cross-reactive and shared the same mol. wt., N-terminal amino acid sequence, and capacity to stimulate rabbit splenocyte proliferation nonspecifically.

L20 ANSWER 29 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 19
ACCESSION NUMBER: 1989:148836 CAPLUS
DOCUMENT NUMBER: 110:148836
TITLE: Nucleotide sequence of **streptococcal** pyrogenic **exotoxin** type **C**
AUTHOR(S): Goshorn, Stephen C.; **Schlievert, Patrick M.**
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Infect. Immun. (1988), 56(9), 2518-20
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The nucleotide sequence of the gene **speC**, encoding **streptococcal** pyrogenic **exotoxin** type **C** (**SPE C**), was detd. The gene encoded a mature protein of 208 amino acids, with a calcd. mol. wt. of 24,354. The mature amino acid sequence of **SPE C** was analyzed

for homol. with the amino acid sequences of **streptococcal** pyrogenic exotoxin type A, the staphylococcal enterotoxins, and toxic shock syndrome toxin-1. Of these, **SPE C** shared the greatest amt. of homol. with **streptococcal** exotoxin type A.

L20 ANSWER 30 OF 44 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 88114036 MEDLINE
DOCUMENT NUMBER: 88114036
TITLE: Cross-neutralization of staphylococcal and streptococcal pyrogenic toxins by monoclonal and polyclonal antibodies.
AUTHOR: Bohach G A; Hovde C J; Handley J P; **Schlievert P M**
CORPORATE SOURCE: Department of Microbiology, University of Minnesota Medical School, Minneapolis 55455.
CONTRACT NUMBER: HL36611 (NHLBI)
SOURCE: INFECTION AND IMMUNITY, (1988 Feb) 56 (2) 400-4. Journal code: GO7. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198805
AB We evaluated cross-reactivity of antibodies against staphylococcal and **streptococcal** pyrogenic toxins. Monoclonal antibodies against staphylococcal enterotoxin (ET) C1 and **streptococcal** pyrogenic exotoxin (SPE) A were tested for reactivity with homologous and heterologous pyrogenic toxins in vitro. Ten immunoglobulin G1 anti-ET C1 monoclonal antibodies showed little or no cross-reactivity in an enzyme-linked immunosorbent assay, but many of these could neutralize the mitogenic effect of ET B, SPE A, or both. Two immunoglobulin M anti-ET C1 monoclonal antibodies and eight immunoglobulin M anti-SPE A monoclonal antibodies showed extensive cross-reactivity in the enzyme-linked immunosorbent assay and the mitogenicity neutralization assay. No cross-reactivity was observed with **SPE C** or toxic shock syndrome toxin 1. Rabbits immunized against ET B, ET C1, or SPE A were resistant to challenge with the immunizing toxin. In addition, reciprocal immunity was stimulated by the two ETs, and immunity to SPE A provided protection against ET B but not ET C1. These results show that staphylococcal and **streptococcal** pyrogenic toxins which share sequence homology have common antigenic determinants which may not be detected in Ouchterlony immunodiffusion assays.

L20 ANSWER 31 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 21
ACCESSION NUMBER: 1988:418121 CAPLUS
DOCUMENT NUMBER: 109:18121

TITLE: Cloning and characterization of the gene, **speC**, for pyrogenic exotoxin type C from **Streptococcus** pyogenes
AUTHOR(S): Goshorn, Stephen C.; Bohach, Gregory A.; **Schlievert, Patrick M.**
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: MGG, Mol. Gen. Genet. (1988), 212(1), 66-70
CODEN: MGGEAE; ISSN: 0026-8925
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structural gene of **streptococcal** pyrogenic **exotoxin** type **C** (**SPE C**) was cloned from the chromosome of S. pyogenes strain T18P into Escherichia coli using pBR328 as the vector plasmid. Subcloning enabled the localization of the gene (speC) to a 1.7 kilobase fragment. Partially purified E. coli-derived **SPE C** and purified **streptococcal**-derived **SPE C**, were shown to have the same mol. wt. (23,800) and biol. activities. A DNA probe, prepd. from cloned speC, cross-hybridized with the structural genes of SPE A and SPE B indicating relatedness at the nucleotide level. The speC-derived probe also hybridized to a fragment of CS112 DNA contg. the phage attachment site.

L20 ANSWER 32 OF 44 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1988:342247 BIOSIS
DOCUMENT NUMBER: BR35:37089
TITLE: CLONING CHARACTERIZATION AND NUCLEOTIDE SEQUENCE OF THE STRUCTURAL GENE ENCODING **STREPTOCOCCAL** PYROGENIC **EXOTOXIN** TYPE **C**.
AUTHOR(S): GOSHORN S C; **SCHLIEVERT P M**
CORPORATE SOURCE: DEP. MICROBIOL., UNIV. MINN., MINNEAPOLIS, MINN. 55455.
SOURCE: ANNUAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, MIAMI BEACH, FLORIDA, USA, MAY 8-13, 1988. ABSTR ANNU MEET AM SOC MICROBIOL, (1988) 88 (0), 39.
CODEN: ASMACK. ISSN: 0094-8519.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L20 ANSWER 33 OF 44 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1987:220510 BIOSIS
DOCUMENT NUMBER: BR32:106384
TITLE: CROSS-NEUTRALIZATION OF STAPHYLOCOCCAL AND STREPTOCOCCAL PYROGENIC TOXINS BY POLYCLONAL AND MONOCLONAL ANTIBODIES.
AUTHOR(S): **SCHLIEVERT P M**; BOHACH G A

CORPORATE SOURCE: DEP. MICROBIOL., UNIV. MINNESOTA, MINNEAPOLIS, MINN. 55455.
SOURCE: 87TH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, ATLANTA, GEORGIA, USA, MARCH 1-6, 1987. ABSTR ANNU MEET AM SOC MICROBIOL, (1987) 87 (0), 48. CODEN: ASMACK. ISSN: 0094-8519.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L20 ANSWER 34 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 22
ACCESSION NUMBER: 1980:489862 CAPLUS
DOCUMENT NUMBER: 93:89862
TITLE: Activation of murine T-suppressor lymphocytes by group A streptococcal and staphylococcal pyrogenic exotoxins
AUTHOR(S): **Schlievert, Patrick M.**
CORPORATE SOURCE: Med. Sch., Univ. California, Los Angeles, CA, 90024, USA
SOURCE: Infect. Immun. (1980), 28(3), 876-80
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of group A **streptococcal** pyrogenic **exotoxin** (PE) type **C** and staphylococcal PE on the in vitro antibody response to sheep erythrocytes was studied in cultures of mouse spleen cells. Both exotoxins suppressed the day 4 direct plaque-forming cell response when added to the cultures. The max. suppression was obtained with 1.0 or 0.1 ng of toxin/culture, and the suppressive effect was reversed by addn. of gangliosides to the cultures at the same time as the exotoxins. Preincubation of T lymphocytes for 4 days with either exotoxin resulted in the generation of a suppressor cell population, which produced dose-dependent suppression of the direct plaque-forming cell response when added to fresh sheep erythrocyte-activated splenocytes. The suppression obtained was not reversed by gangliosides indicating toxin carry-over was not responsible for the effect. B cells, preincubated with exotoxin, failed to suppress the direct plaque-forming cell response of fresh erythrocyte-activated spleen cells.

L20 ANSWER 35 OF 44 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 80203492 MEDLINE
DOCUMENT NUMBER: 80203492
TITLE: Inhibition of ribonucleic acid synthesis by group A streptococcal pyrogenic exotoxin.
AUTHOR: **Schlievert P M**; Bettin K M; Watson D W
SOURCE: INFECTION AND IMMUNITY, (1980 Feb) 27 (2) 542-8.
Journal code: GO7. ISSN: 0019-9567.
Searcher : Shears 308-4994

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198010

AB Group A **streptococcal** pyrogenic exotoxins (SPEs) A, B, and C and alpha-amanitin enhance host susceptibility to lethal endotoxin shock. The capacity of **SPE C** and alpha-amanitin to prepare rabbits for the enhancement phenomenon required pretreatment of the animals 1 to 2 h before giving endotoxin. Endotoxin clearance from the circulation of rabbits pretreated with either **SPE C** or alpha-amanitin was reduced. Even at the time of death, significant amounts of endotoxin remained in the circulation. It is proposed that the SPE and alpha-amanitin inhibit ribonucleic acid synthesis in Kupffer cells with concomitant alteration in reticuloendothelial clearnace function, allowing endotoxin to persist in the circulation and produce host injury. All three SPE types and alpha-amanitin inhibited ribonucleic acid synthesis by 50% or greater in whole liver cells. Kupffer cells, liver cell nuclei, and liver nuclear extracts; inhibition was observed liver cells from both mice and rabbits. The inhibitory effect by SPEs was dose dependent and was observed after as little as 15 min of preincubation with liver cells. The content of ribonucleic acid in liver nuclei of mice pretreated with either **SPE C** or alpha-amanitan was reduced, whereas total deoxyribonucleic acid and protein content remained unaltered.

L20 ANSWER 36 OF 44 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 80136335 MEDLINE
DOCUMENT NUMBER: 80136335
TITLE: Ganglioside and monosaccharide inhibition of nonspecific lymphocyte mitogenicity by group A streptococcal pyrogenic exotoxins.
AUTHOR: **Schlievert P M**; Schoettle D J; Watson D W
SOURCE: INFECTION AND IMMUNITY, (1980 Jan) 27 (1) 276-9.
Journal code: GO7. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198007

AB Group A **streptococcal** pyrogenic exotoxins (SPE) types A, B, and C are potent nonspecific lymphocyte mitogens. The mitogenicity of these exotoxins was inhibited by gangliosides and sialic acid, whereas concanavalin A was unaffected. The capacity of both concanavalin A and SPE-A to stimulate lymphocytes was suppressed by alpha-methyl-D-mannopyranoside. Galactose reduced the activity of **SPE-C**. The sugars, glucose, N-acetylglucosamine, alpha-methyl-D-glucopyranoside, and fucose, did

not affect SPE mitogenicity.

L20 ANSWER 37 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 25
ACCESSION NUMBER: 1980:90548 CAPLUS
DOCUMENT NUMBER: 92:90548
TITLE: Production of pyrogenic exotoxin by groups of streptococci: association with group A
AUTHOR(S): **Schlievert, Patrick M.**; Bettin, Kristine M.; Watson, Dennis W.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: J. Infect. Dis. (1979), 140(5), 676-81
CODEN: JIDIAQ; ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several groups of streptococci were tested for prodn. of pyrogenic exotoxins (SPE) with Ouchterlony immunodiffusion, a newly developed passive hemagglutination inhibition assay, and an assay for pyrogenicity and capacity toenhance lethal endotoxin shock. With use of these assays, 68 (91%) of 75 group A streptococcal strains were pos. for .gtoreq.1 of SPE types A, B, and C; 7 were neg. for both the known SPE types and antigenically unrelated pyrogenic exotoxins. Group A strains producing both SPEB and C were the most common, and strains producing A alone or AB and AC together were the least common. All of 11 rheumatogenic group A **streptococci** elaborated **SPEC** either alone or together with one or both of SPE types A and B. The 10 nephritogenic strains tested were pos. for SPE B; 5 were pos. for B alone. In contrast to group A streptococci, non-group A strains (41 tested) did not produce the known SPE types, and 19 of 19 tested were neg. for antigenically unrelated pyrogenic exotoxins. Group A strains from Holland, India, and Japan also elaborated SPE. Several group A streptococci used widely in lab. expts. were tested for SPE types produced.

L20 ANSWER 38 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 26
ACCESSION NUMBER: 1980:39075 CAPLUS
DOCUMENT NUMBER: 92:39075
TITLE: Natural phosphorylation of group A **streptococcal** pyrogenic **exotoxin** type **C**
AUTHOR(S): **Schlievert, Patrick M.**; Bettin, Kristine M.; Watson, Dennis W.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Infect. Immun. (1979), 26(2), 585-9
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Group A **streptococcal** pyrogenic **exotoxin** (SPE)

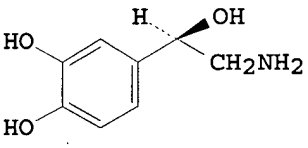
type **C**, produced by strain T18P grown in the presence of 32P, was sepd. from culture supernatant fluids by using alc. pptn. The resulting toxin (EtOH-1) contained 3 .times. 106 to 5 .times. 106 cpm of 32P/mg of protein. The radiolabel migrated with SPE C during isoelec. focusing in polyacrylamide gels (pI 6.7) and double immunodiffusion, in which the toxin formed a line of identity with highly purified SPE C when reacted with hyperimmune antiserum raised against SPE C. The EtOH-1 radiolabeled toxin was pyrogenic and had the capacity to enhance host susceptibility to lethal endotoxin shock. EtOH-1 toxin lost both radiolabel and biol. activity after being treated with alk. phosphatase. The nonsp. lymphocyte mitogenicity of purified unlabeled SPE C was stimulated by AMP but not adenosine, ADP, or ATP. AMP may function as a cofactor of SPE C and contribute the phosphate group required for biol. activity.

L20 ANSWER 39 OF 44 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 80203408 MEDLINE
DOCUMENT NUMBER: 80203408
TITLE: Reinterpretation of the Dick test: role of group A streptococcal pyrogenic exotoxin.
AUTHOR: **Schlievert P M**; Bettin K M; Watson D W
SOURCE: INFECTION AND IMMUNITY, (1979 Nov) 26 (2) 467-72.
Journal code: GO7. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198010

AB Because of the association of the group A **streptococcal** pyrogenic exotoxins (SPEs) with erythrogenic toxin used in the classical Dick test, the involvement of the SPEs in production of erythematous skin reactions was assessed. Unless they had been presensitized, young adult rabbits failed to show skin reactions after intracutaneous challenged with SPEs. Rabbits presensitized to purified protein derivative exhibited enhanced skin reactivity when given purified protein derivative plus **SPE C**; the enhancement was neutralized by antiserum to **SPE C**. Rabbits sensitized to bovine serum albumin showed extensive red rash development resembling scarlet fever rashes when given bovine serum albumin containing **SPE C**. Desquamation occurred 5 to 10 days after injection. Animals sensitized to one SPE type showed enhanced skin reactivity to challenge with homologous or heterologous SPE types, indicating the presence of a cross-reactive determinant within the SPE molecules. Repeated challenge of SPE-sensitized animals with homologous toxin resulted in concomitant antitoxin production with reduction of the enhanced skin reactivities, until typical delayed-hypersensitivity skin reactions remained. The data indicate that, in addition to the toxic reaction previously described, SPEs enhance Arthus and

delayed-hypersensitivity skin reactions. It follows that erythrogenic toxin represents the enhancement of acquired skin reactivity to **streptococcal** antigens by one or more SPE types. Therefore, the Dick test measures SPE-enhanced hypersensitivity to **streptococcal** products.

L20 ANSWER 40 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 28
ACCESSION NUMBER: 1980:35570 CAPLUS
DOCUMENT NUMBER: 92:35570
TITLE: Biogenic amine involvement in pyrogenicity and enhancement of lethal endotoxin shock by group A streptococcal pyrogenic exotoxin
AUTHOR(S): **Schlievert, Patrick M.**; Watson, Dennis W.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Proc. Soc. Exp. Biol. Med. (1979), 162(2), 269-74
CODEN: PSEBAA; ISSN: 0037-9727
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Group A **streptococcal** pyrogenic **exotoxin** type **C (SPE C)** produced fever which in part depended upon norepinephrine bitartrate (I bitartrate) [51-40-1] and stimulation of .alpha.-adrenergic receptors. Intracisternal injection of I into rabbits already showing fevers due to SPE C resulted in further heightened fevers. Pretreatment of animals with either .alpha.-methyltyrosine to deplete I stores or phenoxybenzamine to block .alpha.-receptors depressed SPE-induced pyrogenicity. Pretreatment of animals with p-chlorophenylalanine to deplete serotonin [50-67-9] stores accentuated fevers due to SPE and giving serotonin intracisternally to rabbits with fevers resulted in a significant drop in body temp. This indicated that serotonin exerted a neg. effect on SPE pyrogenicity. Isoproterenol and propranolol did not affect SPE C fever prodn. When used alone, none of the drugs prevented the capacity of SPE C to enhance lethal endotoxin shock. However, phenoxybenzamine in combination with fluid replacement increased the survival rate of rabbits. Thus, SPE C may alter the endotoxin detoxification system, allowing endotoxin

to persist in the circulation producing shock.

L20 ANSWER 41 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 29
ACCESSION NUMBER: 1978:574753 CAPLUS
DOCUMENT NUMBER: 89:174753
TITLE: Group A streptococcal pyrogenic exotoxin: pyrogenicity, alteration of blood-brain barrier, and separation of sites for pyrogenicity and enhancement of lethal endotoxin shock
AUTHOR(S): **Schlievert, Patrick M.**; Watson, Dennis W.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, Minn., USA
SOURCE: Infect. Immun. (1978), 21(3), 753-63
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Group A **streptococcal** pyrogenic **exotoxin** type **C (SPE C)** produced fever by crossing the blood-brain barrier. The toxin directly stimulated the hypothalamic fever response control center, thus bypassing a requirement for endogenous pyrogen release. SPE C was detected in the cerebrospinal fluids of toxin-treated rabbits by pyrogen tests and a hemagglutination inhibition assay. The toxin altered the permeability of the blood-brain barrier to endotoxin, Streptococcus pneumoniae, and Haemophilus influenzae as well as to itself. SPE C did not alter the in vivo differential and total counts of peripheral blood leukocytes and did not elicit endogenous pyrogen release from leukocytes in vitro. In vivo, peripheral blood platelet counts remained unchanged after SPE treatment. Cycloheximide pretreatment of rabbits did not inhibit fever prodn. by SPE C. In contrast to the hypothermia obsd. in mice treated with endotoxin i.v., SPE C given i.v. to mice produced dose-dependent fever and enhanced susceptibility to lethal endotoxin shock. The abilities of SPE C to produce fever and enhance lethal shock were sep. functions of the mol.; fever results from stimulation of the hypothalamus, and enhancement appears not to involve the central nervous system.

L20 ANSWER 42 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 30
ACCESSION NUMBER: 1978:400433 CAPLUS
DOCUMENT NUMBER: 89:433
TITLE: Effect of antipyretics on group A streptococcal pyrogenic exotoxin fever production and ability to enhance lethal endotoxin shock
AUTHOR(S): **Schlievert, P. M.**; Bettin, K. M.; Watson, D. W.
CORPORATE SOURCE: Dep. Microbiol., Univ. Minnesota, Minneapolis, Minn., USA

SOURCE: Proc. Soc. Exp. Biol. Med. (1978), 157(3), 472-5
CODEN: PSEBAA; ISSN: 0037-9727
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The fever response of rabbits to group A **streptococcal** pyrogenic **exotoxin** (SPE) type **C** was effectively reduced by pretreatment of the animals with indomethacin [53-86-1] (25 mg/kg), acetylsalicylate [50-78-2] (200 mg/kg), and cortisone [53-06-5] (5 mg on each of 3 preceding days and 2 h before given SPE). Indomethacin and acetylsalicylate also reduced the fever response of rabbits to SPE type C if given near the time of max. fever response (4 h after SPE). None of the antipyretic agents protected the rabbits from SPE's capacity to enhance susceptibility to lethal endotoxin shock. Apparently, SPE fever prodn. requires prostaglandin synthesis, probably PGE1 or PGE2, and the mechanism of fever prodn. by SPE may be different from the mechanism underlying the enhancement of lethal endotoxin shock.

L20 ANSWER 43 OF 44 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 31
ACCESSION NUMBER: 1977:434214 CAPLUS
DOCUMENT NUMBER: 87:34214
TITLE: Purification and characterization of group A **streptococcal** pyrogenic **exotoxin** type **C**
AUTHOR(S): **Schlievert, Patrick M.**; Bettin, Kristine M.; Watson, Dennis W.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, Minn., USA
SOURCE: Infect. Immun. (1977), 16(2), 673-9
CODEN: INFIBR
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Group A **streptococcal** pyrogenic **exotoxin** (SPE) type **C** was partially purified by differential soly. in EtOH and acetate-buffered saline. Toxin prepd. in this way consisted of protein and hyaluronic acid. After removal of hyaluronic acid, the toxin remained pyrogenic, enhanced susceptibility of rabbits to lethal endotoxin shock, was stable when treated with acid, base, or pepsin, but was inactivated by heat. Toxin further purified by thin-layer isoelec. focusing was pyrogenic and enhanced the susceptibility of rabbits to lethal endotoxin shock. Purified type C toxin appeared homogeneous when tested by Ouchterlony immunodiffusion and migrated as a single protein band in isoelec. focusing polyacrylamide gels (isoelec. point, 6.7) and sodium dodecyl sulfate-polyacrylamide gels (mol. wt., 13,200). The purified toxin was antigenically distinct from A and B SPE, and antisera raised against the purified toxin neutralized pyrogenic activity. The amino acid compn. was detd.

L20 ANSWER 44 OF 44 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1977:48314 BIOSIS
DOCUMENT NUMBER: BR13:48314
TITLE: PURIFICATION AND CHARACTERIZATION OF **STREPTOCOCCAL** PYROGENIC **EXO** **TOXIN** TYPE **C**.
AUTHOR(S): **SCHLIEVERT P M**; BETTIN K M; WATSON D W
SOURCE: Abstr. Annu. Meet. Am. Soc. Microbiol., (1977) 77, 26.
CODEN: ASMACK. ISSN: 0094-8519.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: Unavailable

=> fil hom

FILE 'HOME' ENTERED AT 14:18:06 ON 24 SEP 1999